Self-Assembly of Bidentate Ligands for Combinatorial Homogeneous Catalysis: Asymmetric Rhodium-Catalyzed Hydrogenation

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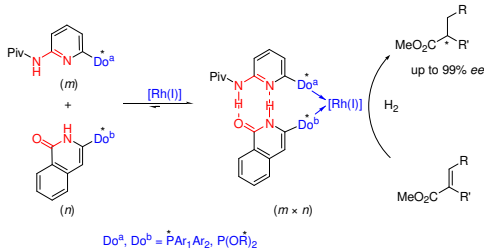
Introduction

Combinatorial methods have recently been introduced to homogeneous metal complex catalysis as a means to accelerate the catalyst discovery process.[1] Many elegant solutions for high throughput screening have been developed.[2] However, so far the combinatorial approach to catalyst discovery and optimization suffers from the limited access to structurally diverse and meaningful ligand libraries. The problem is particularly acute for the important class of bidentate ligands, due to the complexity of bidentate ligand synthesis. In many cases non-trivial synthetic operations are required, which render the ligand synthesis unsuited for automation. A particular challenge is the synthesis of nonsymmetric bidentate ligands equipped with two different donor sites.

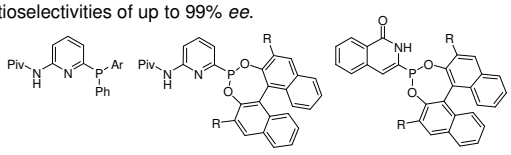


Scheme 1: Self-assembly of chiral monodentate to chiral bidentate ligands through complementary hydrogen-bonding for combinatorial asymmetric catalysis.

We recently introduced an alternative to the classical covalent bidentate ligand synthesis, which relies on self-assembly of monodentate ligands through complementary hydrogen-bonding to give defined heterodimeric bidentate ligands on the basis of an A-T base pair analogue, the aminopyridine-isoquinolone system (Scheme 1).[3,4]

Results

We herein report on the application of a new library of chiral aminopyridine and isoquinolone systems equipped with phosphine and phosphonite donors (Scheme 2) to the asymmetric rhodium-catalyzed hydrogenation. From this chiral ligand library new heterodimeric combinations emerged, which furnished catalysts performing with enantioselectivities of up to 99% *ee*.



(–)-**1a**: Ar = *o*-Anisyl
(+)-**1a**: Ar = *o*-Anisyl
(–)-**1b**: Ar = 1-Naphthyl
(+)-**1b**: Ar = 1-Naphthyl
(–)-**1c**: Ar = *o*-Tol
(+)-**1c**: Ar = *o*-Tol

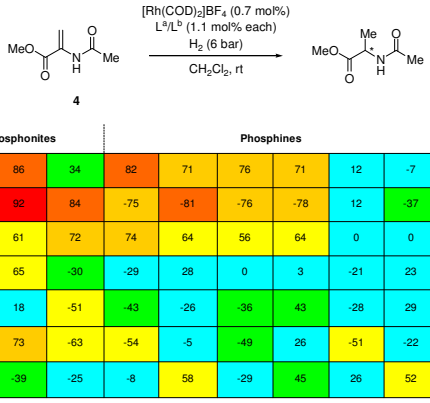
(*S*)-**2a**: R = H
(*S*)-**2b**: R = Me
(*S*)-**2c**: R = *p*-Tol

(*S*)-**3a**: R = H
(*R*)-**3a**: R = H
(*S*)-**3b**: R = Me

Scheme 2: Library of chiral aminopyridine and isoquinolone ligands.

Original catalyst screening was done for the rhodium-catalyzed hydrogenation of acetamidoacrylate using a Chemspeed Accelerator™ (Scheme 3 and 4).

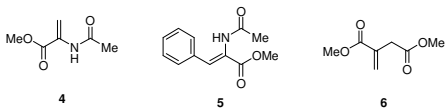
Scheme 3: Chemspeed Accelerator™.



Scheme 4: Asymmetric hydrogenation of acetamidoacrylate: High throughput screening of a 9×7 matrix.

The most interesting ligand pairs from the screening of this 9x7 matrix were investigated further. A small sublibrary based on the bisphosphonite systems was screened in the asymmetric hydrogenation of methyl-α-acetylamino cinnamate (**5**) and dimethylitaconate (**6**) (Table 1).[5]

Table 1. Rhodium-catalyzed hydrogenation of methyl-α-acetamidoacrylate (**4**), acetylamino cinnamate (**5**) and dimethylitaconate (**6**).



	ligands	subst.	s/c	solvent	t	p [bar]	*ee* [%]
1	(+)-**1a**/(*S*)-**3a**	4	100	DCM	rt	1	92(*R*)
2	*idem*	4	100	1,2-DCE	0°C	1	94(*R*)
3	(*S*)-**2a**/(*S*)-**3b**	4	100	DCM	rt	1	92(*R*)
4	(*S*)-**2a**/(*S*)-**3a**	4	100	DCM	rt	1	97(*R*)
5	*idem*	4	100	1,2-DCE	rt	1	98(*R*)
6	*idem*	4	1000	DCM	rt	1	99(*R*)
7	*idem*	5	100	DCM	rt	6	94(*S*)
8	(*S*)-**2b**/(*S*)-**3a**	5	100	DCM	rt	30	94(*R*)
9	(*S*)-**2a**/(*S*)-**3b**	6	100	DCM	rt	1	94(*R*)

These results indicate that catalyst/ligand adjustment to a particular substrate of interest is an important issue, and a combinatorial approach based on self-assembly is in fact a useful technique in order to rapidly identify an optimal catalyst.

Conclusion

In conclusion, the first chiral bidentate phosphorus donor ligand library based on self-assembly through hydrogen bonding was screened in the rhodium-catalyzed asymmetric hydrogenation. Bidentate ligand combinations of phosphine/phosphonites, as well as diphosphonite systems, were identified which furnhished excellent catalysts performing with enantioselectivities of up to 99% *ee*. Application of this and other chiral ligand libraries to asymmetric catalysis is ongoing in these laboratories.

References

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Acknowledgments

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